Palonosetron and netupitant for prevention of chemotherapy-induced nausea and vomiting

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The US Food and Drug Administration (FDA) recently approved NEPA, an oral fixed-dose combination of netupitant and palonosetron for treatment of chemotherapy-induced nausea and vomiting (CINV). Palonosetron is a pharmacologically distinct, best-in-class serotonin (5-hydroxytryptamine) type 3 (5-HT_3) receptor antagonist, which prevents CINV during the acute phase (0-24 h) after administration of chemotherapy, and netupitant is a potent and selective neurokinin-1 (NK-1) receptor antagonist, which prevents CINV during both the acute and delayed (25-120 h) phases. The 2 agents have also been shown potentially to act synergistically in inhibiting NK-1 receptor activity.

The results of 2 pivotal, multicenter, randomized, double-blind, double-dummy, parallel-group studies that demonstrated superior complete response (CR) rates (defined as no vomiting [emesis] and no need for rescue medication) were used as the basis for the October 2014 FDA approval; a phase 3 trial conducted at 177 sites in 15 countries during April 2011-November 2012, and a phase 2 trial conducted at 29 sites in Russia and 15 sites in Ukraine in 2008.

In the phase 2 trial, 694 chemotherapy-naïve patients aged 18 years or older, with a Karnofsky Performance Scale score of ≥70% (70 = cares for self; unable to carry on normal activity or to do active work) and who were scheduled to receive their first course of highly emetogenic chemotherapy (cisplatin-based chemotherapy at a dose of ≥50 mg/m^2 alone or in combination with other chemotherapeutic agents) were randomized 1:1 to 1 of 5 treatment groups that compared palonosetron (0.5 mg) in combination with dexamethasone (20 mg) and placebo with 3 different doses of netupitant (100, 200, and 300 mg) in combination with palonosetron (0.5 mg) and dexamethasone (12 mg), as well as a fifth exploratory arm evaluating a different NK-1 and 5-HT_3 receptor antagonist combination of aprepitant, ondansetron, and dexamethasone, all administered before chemotherapy on day 1. Dexamethasone was also administered on days 2-4 at a dose of 8 mg BID in the palonosetron arm and 4 mg BID in the NEPA arms. Randomization was stratified by gender.

In the phase 3 trial, 1,455 chemotherapy-naïve patients aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and who were scheduled to receive their first course of moderately emetogenetic chemotherapy (anthracyclin-cyclophosphamide-based regimen) were randomized 1:1 to NEPA (netupitant 300 mg and palonosetron 0.5 mg) plus dexamethasone (12 mg) or palonosetron (0.5 mg) plus dexamethasone (20 mg) on day 1 before chemotherapy. Randomization was stratified by region and age class.

Ineligibility criteria for the 2 studies were similar and included patients scheduled to receive additional moderately/highly emetogenic chemotherapy on days 2-5, or moderately/highly emetogenic radiation therapy within 1 week before day 1 or from day 2-5, or bone marrow or stem-cell transplant, or drugs with known antiemetic activity within 24 hours of day

What's new, what's important

In recent years, the optimal management and control of CINV has risen to top priority for patients and providers. This shift has been driven by changes in attitudes among both providers and patients. But one of the most important clinical developments has been the gradual evolution of 5-HT_3 receptor antagonists and the development of NK-1 inhibitors.

Currently, the most commonly used regimen for highly emitogenic chemotherapy is a combination of the 5-HT_3 receptor antagonist, palonosetron; the NK-1 inhibitor, aprepitant; plus dexamethasone. Then last fall, the FDA approved NEPA, an oral, fixed-dose combination containing 300 mg of netupitant, a highly selective NK1 receptor antagonist, and 0.50 mg of palonosetron, a pharmacologically and clinically distinct 5-HT_3 receptor antagonist, for the prevention of CINV. This new combination drug offers a single pill alternative to previous multiagent antiemetic regimens that are the current standard of care for the prevention of CINV. In the 2 trials that formed the basis of the approval, treatment-related AEs were comparable for incidence, type, frequency, and intensity between the study and control arms, with headache and constipation being the most common.

In this era of value-based care, treatment selection is based on a range of factors, including efficacy, safety, and cost. Published studies have shown similar or superior efficacy with current regimens, and comparable cost. NEPA is an excellent option for the prevention of CINV.

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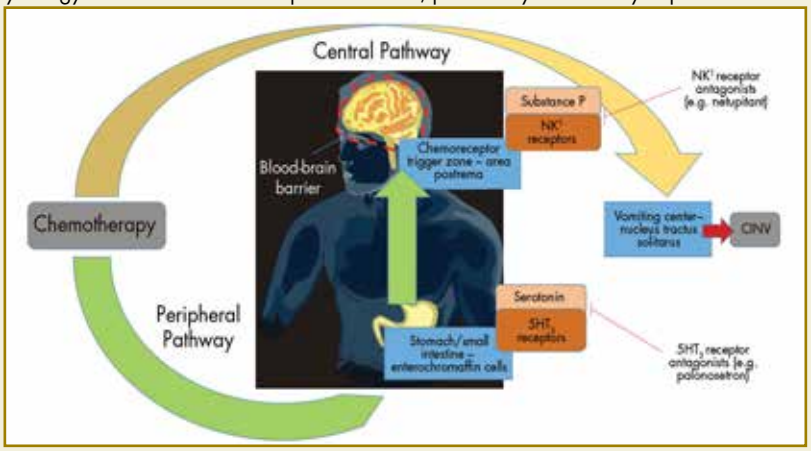
Targeting 2 critical pathways of CINV

Several molecular pathways are involved in the physiology of nausea and vomiting, 2 of which (the central and peripheral pathways) are thought to be particularly important in the pathophysiology of CINV. Both pathways lead to the vomiting center, a neural network found in the nucleus tractus solitarus region of the brain.

The precise molecular mechanisms are significantly more complex, but in the simplest terms, the central pathway involves the chemoreceptor trigger zone (CTZ), located in the area postrema outside the blood-brain barrier, where it acts as an entry point to the brain for nausea and vomiting (also known as emesis) signals. The peripheral pathway predominantly involves the enterochromaffin cells found in the gastrointestinal tract, but this ultimately also signals to the CTZ.

Numerous neurotransmitters and their pathways are involved in propagating the emetogenic signals in these pathways. In the CTZ, this primarily involves the neurotransmitter substance P and neurokinin-1 (NK-1) receptors, while the enterochromaffin cells predominantly respond to chemotherapy by releasing serotonin, which binds to serotonin (5-hydroxytryptamine) type 3 (5-HT_3) receptors. These receptors are located on structures throughout the gastrointestinal tract, brain, and on the nerves that signal between the 2, and it is believed there is significant cross-talk between them. Ultimately, they stimulate the vomiting center, which initiates the physical response of vomiting.

Given the role of these receptors in emesis control, there has been significant focus on the development of antagonists of the receptors to treat CINV and these agents have become standard of care; in patients being treated with moderately emetogenic chemotherapy, current standard of care is palonosetron in combination with the corticosteroid dexamethasone, and for highly emetogenic chemotherapy, the same regimen is used with the addition of an NK-1 receptor antagonist. These regimens are recommended in treatment guidelines, however these are poorly adhered to and many patients continue to experience CINV, particularly in the delayed phase.



Palonosetron is a 5-HT_3 receptor antagonist, first approved in an oral formulation in 2008, and has been shown to prevent nausea and vomiting in the acute phase. It is pharmacologically distinct from other 5-HT_3 receptor antagonists in that it has a longer half-life in the plasma (>40 h), thus inhibiting receptor function for longer, and it binds to the receptor differently to other antagonists and with higher affinity. In addition, in vitro study findings have suggested that it may inhibit intracellular crosstalk between 5-HT_3 and NK-1 receptors. While the former result in its clinical superiority as a single agent, the latter is proposed to result in synergistic activity when combined with NK-1 receptor antagonists. Indeed, a combination of palonosetron and netupitant resulted in a greater inhibition of the substance P response than either agent alone.

Netupitant is a novel, highly selective inhibitor of NK-1, which blocks the substance P-mediated response to chemotherapy and prevents CINV in both the acute and delayed phase. NEPA combines the 2 drugs in a single oral capsule and thus prevents nausea and vomiting across the acute and delayed phases with a single dose, which it is hoped will improve convenience and adherence to guideline recommendations.

1. Patients who experienced vomiting, retching or mild nausea within 24 hours of day 1, patients with serious cardiovascular disease, or those with a history of cardiac conduction abnormalities were also excluded. Patient demographics and baseline characteristics were well balanced in both studies.

Patients completed diaries on the timing and duration of emetic episodes, which were defined as a single vomiting occurrence, a single retching, or any retching combined with vomiting, and the severity of nausea was evaluated on a daily basis using a 100 mm horizontal visual analog scale (0 = no nausea; 100 = nausea as bad as it could be). The primary endpoint was CR during the overall phase for the phase 2 study and during the delayed phase for the phase 3 study and secondary endpoints included CR during other phases, no emesis, no significant nausea and complete protection (CR and no significant nausea).

All NEPA doses evaluated in the phase 2 trial demonstrated superior CR rates to the palonosetron arm during the delayed and overall phases, and a 300 mg dose was also superior in the acute phase. The 300 mg dose was also more beneficial than the lower doses across all secondary endpoints and had higher rates of no emesis, no significant nausea, and complete protection compared with palonosetron across all phases. This provided the rationale for the study of a 300 mg dose in the subsequent phase 3 study, in which it also demonstrated superiority to palonosetron in both the primary endpoint (CR delayed phase: 76.9% vs 69.5%; P = .001) and several secondary endpoints (CR

How we treat CINV

At Mayo Clinic, antiemetic guidelines have been standardized in the chemotherapy electronic ordering system. Each chemotherapy treatment has an emetogenic potential assigned and that dictates the recommended antiemetic regimen that should be used. By using this system, we obtain more than 90% compliance with recommendations.[1]

We presently treat patients who are receiving highly emetogenic regimens (including doxorubicin plus cyclophosphamide for breast cancer) with triple therapy of serotonin (5-hydroxytryptamine) type 3 receptor antagonist (5HT3 RA), neurokinin-1 receptor antagonist (NK1 RA), plus corticosteroid, consistent with NCCN and ASCO guidelines. We use granisetron as our standard 5HT3 RA. We recommend palonosetron as the 5HT3 RA for patients who are receiving high-dose cisplatin (>75 mg/m2) or for those with poor control of nausea and vomiting after highly emetogenic chemotherapy with standard therapy.

With regard to choice of NK1 RA, our practice is to use fosaprepitant. The notable exception is with use of anthracycline-containing regimens, particularly doxorubicin plus cyclophosphamide, where IV fosaprepitant has been associated with an increased risk of infusion site reactions and pain.[2] Thus, for highly emetogenic anthracycline-containing regimens, we use oral aprepitant.

Olanzapine is not, at this time, standardly used at the Mayo Clinic in the setting of prophylactic regimens for CINV. It is commonly recommended by our palliative care colleagues for refractory nausea and vomiting and is an excellent choice for patients with refractory symptoms.

— Collin T Zimmerman, MD, and Timothy J Moynihan, MD

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acute phase: 88.4% vs 85%; CR overall phase 74.3% vs 66.6%; *P* = .047 and .001, respectively). Of note is that no other drug combination has been shown to improve nausea control, but in the NEPA group in this trial a significantly greater number of patients experienced no significant nausea during the delayed and overall phases.

The data reported in these clinical trials were for 1 cycle of chemotherapy, however, the prescribing information highlights a third trial (n = 309) in which the safety and efficacy of NEPA were confirmed over multiple cycles of chemotherapy. A fourth trial (n = 739) noted in the prescribing information demonstrated the noninferiority of oral palonosetron to intravenous palonosetron and showed that palonosetron contributes to the efficacy of NEPA in the acute phase.

In both pivotal trials there were few adverse events and those that occurred were mostly mild-to-moderate in severity, with fewer than 1% of patients experiencing severe AEs in the NEPA arm. The incidence, type, frequency, and intensity of treatment-related AEs was comparable between the 2 arms; most common in the phase 3 trial were headache (3.3% vs 3%) and constipation (2.1% vs 2.1%). There were no cardiac safety concerns based on AEs and electrocardiogram results.

According to the prescribing information for NEPA, the dose for patients receiving highly emetogenic chemotherapy is 1 capsule (300 mg netupitant, 0.5 mg palonosetron) administered 1 hour before the start of chemotherapy, with dexamethasone 12 mg administered orally 30 minutes prior on day 1 and 8 mg QD on days 2-4. In patients receiving chemotherapy that is not considered to be highly emetogenic or receiving anthracycline-cyclophosphamide-based chemotherapy, 1 capsule should be administered 1 h before the start of chemotherapy, with dexamethasone 12 mg administered 30 minutes prior on day 1. There are warnings and precautions about possible hypersensitivity reactions and serotonin syndrome, especially when NEPA is administered concurrently with other serotonergic drugs. Caution should be used in patients receiving concomitant medications that are metabolized primarily through CYP3A4, and the use of NEPA should be avoided in patients receiving strong CYP3A4 inhibitors. The safety and efficacy of NEPA has not been established in patients who are younger than 18 years.

CINV adversely affects patient quality of life and may have an impact on treatment decisions. Despite the availability of effective anti-emetic combination regimens that are recommended in treatment guidelines, many patients still experience CINV, particularly in the delayed phase. NEPA, marketed as Akynzeo by Eisai Inc, represents an important option, providing a convenient single-dose regimen, with sufficient efficacy to prevent CINV through 5 days after chemotherapy.

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